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Force–interval relationship predicts mortality in survivors of myocardial infarction with atrial fibrillation ☆

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ABSTRACT

Background: : RR interval variations lead to beat-to-beat blood pressure differences through the myocardial force–interval relationship (FIR). In sinus rhythm, an altered FIR leads to post-extrasystolic potentiation (PESP) of systolic blood pressure, which has been shown to predict adverse outcome in survivors of acute myocardial infarction (MI). The purpose of this study was (1) to develop a parameter to assess the FIR in patients with atrial fibrillation (AF) and (2) to investigate its association with mortality in MI survivors suffering from AF.

Methods and results: : Thirty-two patients with acute MI and AF underwent 30-min recordings of ECG and continuous blood pressure. Episodes of a short RR interval (<80% of mean interval, RR_i) preceding a long interval (>140%, RR_{i+1}) were identified. The systolic pressures of the pulse waves following RR_i and RR_{i+1} were labeled P_i and P_{i+1}. $PESP_{Afib}$ was calculated as $(P_{i+1} - P_i) / (RR_{i+1} - RR_i)$.

During 5 years of follow-up, 13 patients died. When $PESP_{Afib}$ was dichotomized at the median, mortality rates were 63% and 19% in patients with high and low $PESP_{Afib}$. Hazard ratio for mortality was 4.88 for patients with high $PESP_{Afib}$ (1.33–17.84, $p = 0.004$). The association of $PESP_{Afib}$ and mortality was independent from LVEF, age, diabetes mellitus or mean heart rate.

Conclusions: : $PESP_{Afib}$, a measure for the FIR in patients with AF, can be derived from simultaneous ECG and blood pressure recordings. The results of this pilot study indicate that $PESP_{Afib}$ may be useful to predict adverse outcome in survivors of myocardial infarction suffering from AF.

1. Introduction

It has been known for more than a century that the contractile force of the first heartbeat after a premature ventricular contraction (PVC) is augmented [1,2]. This phenomenon is termed post-extrasystolic potentiation (PESP) [3,4]. Recently, we reported that PESP, measured at the blood pressure level, is a powerful and independent predictor of mortality in survivors of myocardial infarction (MI) [5].

Substantial beat-to-beat variations of RR interval durations, similar in their extent to PVC coupling intervals and compensatory pauses, occur also during atrial fibrillation (AF). This allows one to modify the concept of PESP for evaluating beat-to-beat blood pressure changes during AF ($PESP_{Afib}$). RR sequences of a short interval followed by a long interval can elicit more or less pronounced augmentations of contractility [6]. We hypothesized that $PESP_{Afib}$ bears prognostic information in MI survivors presenting with AF.

2. Methods

2.1. Study cohort

During the screening period of the Autonomic Regulation Trial (ART) [5], we identified 32 patients suffering from acute myocardial infarction (MI) who were excluded from the ART study analyses because of AF [5]. These patients comprised the study cohort of the present analysis.

MI was diagnosed based on the presence of at least two of the following findings: (1) typical chest pain for at least 20 min, (2) creatine kinase above twice the upper normal limit, and (3) ST-segment elevation ≥ 0.1 mV or ≥0.2 mV in at least two contiguous limb or precordial leads, respectively. AF was diagnosed in the resting ECGs based on tracings with no P waves, with fibrillatory waves of different amplitudes and duration, and with irregular ventricular response. Patients with the indication for secondary-prophylactic cardioverter-defibrillator (ICD) implantation before hospital discharge were excluded. Written informed consent was obtained from all participants. The study protocol conforms to the ethical principles of the 1975 Declaration of Helsinki and was approved by the local ethics committee.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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The predefined primary study endpoint was all-cause mortality at five years after the index MI. Clinical follow-up appointments were scheduled every 6 months. If a patient did not attend a planned appointment, contact was made via telephone, mail or through the attending general practitioner. If none of these channels were successful, the local population registry was contacted to either receive the patient's new address or confirm that the patient had deceased.

2.2. Measurements

Patients underwent simultaneous 30-min recordings of high resolution ECG (sampled at 1.6 kHz in orthogonal XYZ leads, TMS International, Enschede, the Netherlands) and finger photoplethysmographic non-invasive continuous arterial blood pressure monitoring (sampled at 200 Hz with a resolution of 1 mm Hg, FMS, Amsterdam, the Netherlands). The recordings were made in supine resting position after routine administration of morning medication. The raw signals were verified by an experienced technician, and artifacts were eliminated where necessary. Left ventricular ejection fraction (LVEF) was assessed by either left ventricular angiography or by biplane echocardiography (Sonos 5500, Hewlett Packard, Palo Alto, CA, USA), based on endsystolic and enddiastolic images from a representative heartbeat.

2.3. Quantification of $PESP_{Afib}$

All QRS complexes that were not marked as artifacts (i.e. also broad QRS complexes resulting from either ventricular premature beats or aberrantly conducted beats) were considered in the following analysis. For each heartbeat, the average RR interval ($\overline{RR}$) of 17 surrounding heartbeats (RR_{i-8}, RR_i, RR_{i+8}) was calculated. Each RR interval was expressed as percentage of $\overline{RR}$. Successive heartbeats qualified for $PESP_{Afib}$ assessment if RR_i was <80% of $\overline{RR}$ and RR_{i+1} was ≥140% of $\overline{RR}$ (Fig. 1A–C), in analogy of short–long sequences elicited by PVCs that are used to calculate PESP in patients with sinus rhythm [5].

The systolic pressures of the pulse waves following RR_i and RR_{i+1} were labeled as P_i and P_{i+1}. $PESP_{Afib}$ was calculated as $(P_{i+1} - P_i) / (RR_{i+1} - RR_i)$, i.e. by relating the systolic pressure change to the RR interval change (Fig. 1D). If more than one RR interval sequence qualified for $PESP_{Afib}$ evaluation, $PESP_{Afib}$ values were averaged.

2.4. Clinical data

Complete revascularization at the time of the $PESP_{Afib}$ measurement was assessed from the cardiac catheterization reports and defined as no remaining stenosis of 75% or more in any main coronary artery. Repeat revascularization was defined as any percutaneous coronary intervention or coronary artery bypass surgery within 1 year of the index infarction.

2.5. Statistics

Continuous variables are presented as median and inter-quartile range (IQR) and were compared using Mann–Whitney's U test. Categorical data are expressed as absolute frequencies and percentages. Cox proportional hazards models and receiver operating characteristic (ROC) curves were used to assess the prognostic value of mortality predictors. Survival curves were estimated with the Kaplan–Meier method and compared with the log-rank test. Differences were considered statistically significant if $p < 0.05$. All statistical analyses were done using IBM SPSS Statistics 20.0 and R 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Median follow-up was 5 years. The clinical characteristics of the study cohort are presented in Table 1. During 5 years of follow-up, 13 patients (41%) died. Of these deaths, six were classified as cardiac deaths

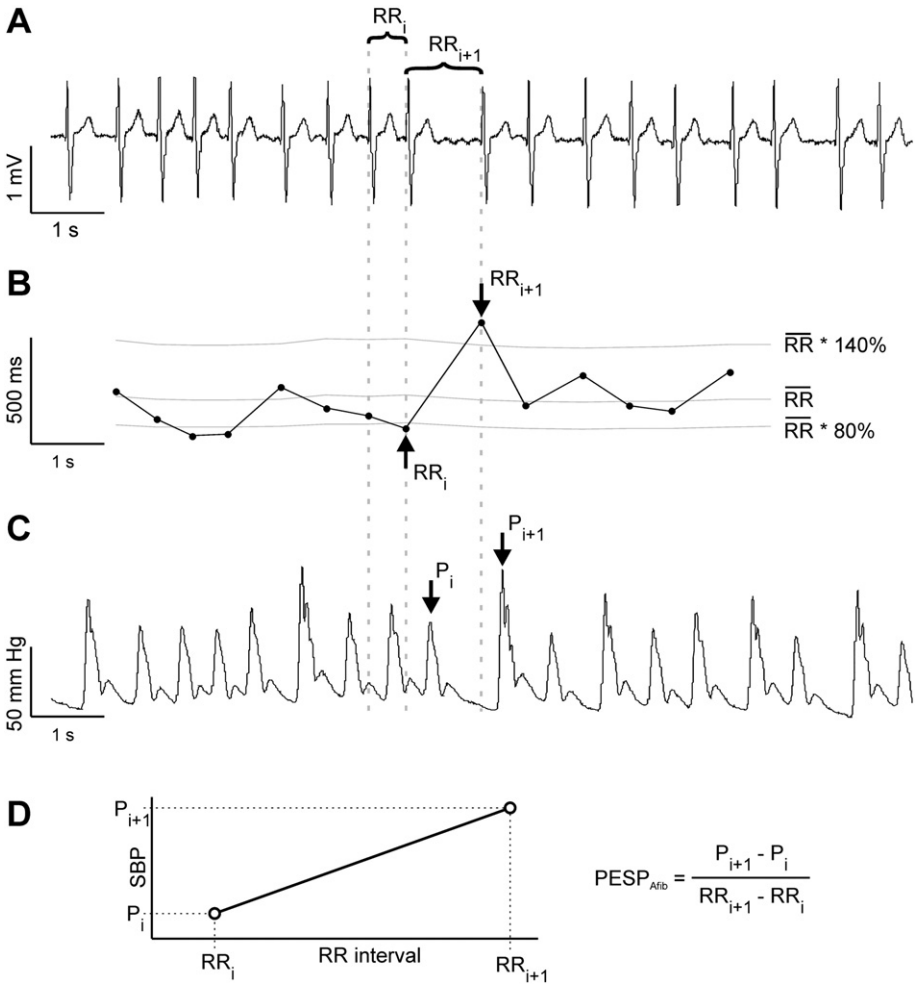

Fig. 1. Quantification of $PESP_{Afib}$ from simultaneous ECG and blood pressure recordings. A representative ECG recording (A), RR interval plot calculated from the ECG (B) and blood pressure recording (C). In the selected segment of the recording, one sequence of RR intervals (denoted RR_i and RR_{i+1}) fulfills the criterion that RR_i is shorter than 80% and RR_{i+1} is longer than 140% of the average RR interval of the 17 surrounding heartbeats ($\overline{RR}$). The line defined by RR_i and RR_{i+1} and the corresponding systolic blood pressure values P_i and P_{i+1} are shown in panel (D), together with the formula of $PESP_{Afib}$ calculation.

Table 1
Baseline characteristics.

Variable	Study cohort (n = 32)	Survivors (n = 19)	Non-survivors (n = 13)
Clinical data			
Age (years), median (IQR)	76 (73–82)	75 (70–81)	80 (73–85)
Females, n (%)	10 (31.3)	6 (31.6)	4 (30.8)
Diabetes mellitus, n (%)	13 (40.6)	7 (36.8)	6 (46.2)
History of previous MI, n (%)	4 (12.5)	3 (15.8)	1 (7.7)
CK max (U/l), median (IQR)	1193 (574–2398)	1336 (539–2878)	1193 (572–1415)
LVEF (%), median (IQR)	42 (31–51)	43 (32–58)	36 (27–49)
Creatinine (mg/dl), median (IQR)	1.2 (1.0–1.4)	1.1 (0.9–1.4)	1.3 (1.1–1.9)
NYHA I, n (%)	17 (51.5)	10 (52.6)	7 (53.8)
NYHA II, n (%)	9 (27.3)	5 (26.3)	4 (30.8)
NYHA III, n (%)	3 (9.1)	2 (10.5)	1 (7.7)
NYHA IV, n (%)	3 (9.1)	2 (10.5)	1 (7.7)
Mean heart rate (bpm), median (IQR)	74 (66–87)	72 (67–84)	81 (64–91)
Anterior infarction, n (%)	9 (28.1)	8 (42.1)	1 (7.7)
Inferior infarction, n (%)	17 (53.1)	8 (42.1)	9 (69.2)
Lateral infarction, n (%)	4 (12.5)	1 (5.3)	3 (23.1)
Paroxysmal atrial fibrillation, n (%)	10 (31.1)	5 (26.3)	5 (38.5)
Persistent/permanent atrial fibrillation, n (%)	2 (68.8)	14 (73.7)	8 (61.5)
Peripheral artery disease, n (%)	2 (6.3)	1 (5.3)	1 (7.7)
Therapy data			
PCI, n (%)	25 (78.1)	15 (78.9)	10 (76.9)
Thrombolysis, n (%)	1 (3.1)	1 (5.3)	0 (0)
CABG, n (%)	0 (0)	0 (0)	0 (0)
No intervention possible/necessary, n (%)	6 (18.8)	3 (15.8)	3 (23.1)
Complete revascularization, n (%)	11 (34.4)	7 (36.8)	4 (30.8)
Repeat revascularization, n (%)	11 (34.4)	7 (36.8)	4 (30.8)
Aspirin, n (%)	30 (93.8)	17 (89.5)	13 (100)
Beta-blockers, n (%)	29 (90.6)	17 (89.5)	12 (92.3)
ACE Inhibitors, n (%)	29 (90.6)	16 (84.2)	13 (100)
Statins, n (%)	28 (87.5)	15 (78.9)	13 (100)
Diuretics, n (%)	23 (71.9)	12 (63.2)	11 (84.6)
Digitalis, n (%)	2 (6.3)	2 (10.5)	0 (0)
Class I/III antiarrhythmics, n (%)	0 (0)	0 (0)	0 (0)

ACE denotes angiotensin-converting enzyme; CABG, coronary artery bypass grafting; CK, creatine kinase; IQR, inter-quartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; PCI, percutaneous coronary intervention.

(two due to heart failure, two due to re-infarction, one ruptured myocardial aneurysm, one sudden cardiac death). Two deaths were classified as non-cardiac deaths (both due to pneumonia with secondary complications). The precise cause of death of the remaining five deceased patients is unknown.

On average, 14 (median, interquartile range 5–32) successive heartbeat pairs met the requirements for $PESP_{Afib}$ calculation. In survivors and non-survivors, the number was 14 (4–33) and 18 (6–32), respectively. Fig. 2 shows the $PESP_{Afib}$ values of all survivors and non-survivors. The five patients with the largest values died, while the seven patients with the lowest values survived. The difference between $PESP_{Afib}$ values of survivors (median 1.7, IQR −1.8–7.4) and non-survivors (median 15.6, IQR 2.2–32.0) was statistically significant ($p = 0.007$). The area under the ROC curve (AUC) was 0.78 (95% confidence interval 0.61–0.94), indicating a good discrimination between survivors and non-survivors.

In univariable Cox proportional hazards analysis, $PESP_{Afib}$ was significantly associated with mortality, while LVEF, age, the presence of diabetes mellitus and the mean heart rate were not (Table 2). The hazard ratio for a 1 mm Hg/s increase in $PESP_{Afib}$ was 1.05 (1.06–1.09, $p = 0.004$, see Table 2). The increase in mortality with increasing $PESP_{Afib}$ cutoff values was almost linear over the range of observed $PESP_{Afib}$ values (Fig. 3).

When $PESP_{Afib}$ was dichotomized at its median (4.5 mm Hg/s), patients with larger $PESP_{Afib}$ had a mortality rate of 63% (10/16), compared to a rate of 19% (3/16) in patients with smaller $PESP_{Afib}$. Kaplan–Meier curves for all-cause mortality in these patient groups are depicted in Fig. 4. The difference between groups was statistically significant ($p = 0.008$). The hazard ratio for $PESP_{Afib} \geq 4.5$ mm Hg/s was 4.88 (1.33–17.84, $p = 0.004$, see Table 2).

The association of $PESP_{Afib}$ with mortality was independent from established risk factors. The low number of events precluded us from performing a factual multivariable Cox analysis including all candidate prognostic parameters. However, when $PESP_{Afib}$ was entered together with either LVEF, age, presence of diabetes mellitus or mean heart rate in a pairwise fashion into multivariable Cox models, $PESP_{Afib}$ consistently remained significantly associated with mortality (Fig. 5).

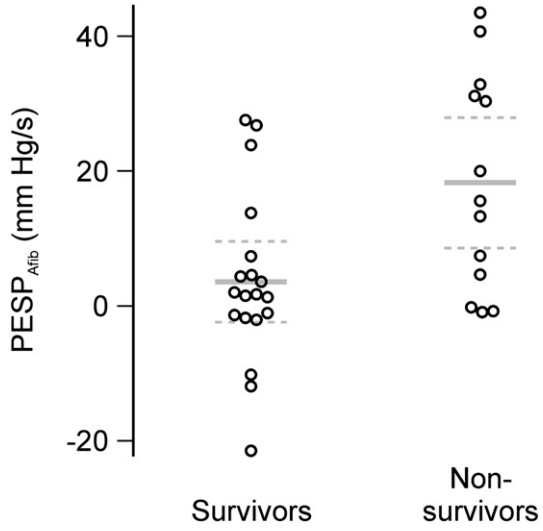

Fig. 2. $PESP_{Afib}$ in survivors and non-survivors. $PESP_{Afib}$ values from individual patients are shown as black circles. Average $PESP_{Afib}$ values and standard deviations are shown as solid and dashed gray lines, respectively.

Table 2
Univariable Cox regression analysis.

Variable		Hazard ratio	χ^2	p
$PESP_{Afib}$	Per 1 mm Hg/s	1.06 (1.02–1.09)	8.37	0.004
	≥4.5 mm Hg/s	4.88 (1.33–17.84)	5.73	0.017
LVEF	Per %	0.96 (0.92–1.00)	2.62	0.106
	≤35%	1.48 (0.48–4.53)	0.47	0.495
Presence of diabetes mellitus		1.22 (0.41–3.62)	0.12	0.725
Age	Per year	1.06 (0.98–1.15)	2.08	0.149
	≥65 years	1.25 (0.16–9.59)	0.04	0.833
Mean heart rate	Per bpm	1.04 (0.98–1.09)	1.56	0.212
	>75 bpm	2.73 (0.91–8.18)	3.23	0.072

Afib denotes atrial fibrillation; bpm, beats per minute; LVEF, left ventricular ejection fraction; PESP, post-extrasystolic potentiation.

To investigate the reproducibility of $PESP_{Afib}$, we divided the 30-minute recording period of each patient into two consecutive 15-minute segments that were separately analyzed. Twenty-nine patients had short–long sequences suitable for $PESP_{Afib}$ calculation in both segments. In each segment, the patient risk was classified as high or low by applying the $PESP_{Afib}$ dichotomy of 4.5 mm Hg/s. The risk classification was concordant in 23 of these patients (79%), indicating reasonable short-term reproducibility.

For the calculation of $PESP_{Afib}$, we did not eliminate broad QRS complexes resulting from PVCs. The average number of PVCs in the 30-minute recordings was 16. Of the short–long sequences used for the calculation of $PESP_{Afib}$, 8.5% were initiated by PVCs. If we excluded PVCs from the analysis, the AUC decreased from 0.78 to 0.73. If $PESP_{Afib}$ was calculated only based on short–long sequences initiated by PVCs, there was no significant association with mortality.

4. Discussion

The main finding of our study is that $PESP_{Afib}$ predicts the outcome of post-MI patients suffering from AF. This observation is in line with the results of our recent report [5] demonstrating that PESP is a strong predictor of mortality in two independent patient cohorts with sinus rhythm, one of MI survivors and one of heart failure patients. Together with previous observations, our data support the concept that evaluating PESP in a clinical setting based on non-invasive continuous blood pressure recordings is suitable to assess the functional status of myocardium for signs of heart failure.

Our observation is potentially clinically important, since in AF patients, the usual non-invasive procedures of risk stratification are of little if any predictive value: Heart rate variability [7], heart rate turbulence [8,9], deceleration capacity of heart rate [10] and T-wave alternans [11] can only be measured during sinus rhythm. Even the assessment of LVEF during atrial fibrillation lacks precision. Other risk predictors such as respiratory rate [12–14] or periodic repolarization dynamics [15] are theoretically applicable in AF patients. However, their prognostic value in AF has not been investigated yet and is thus unknown. A novel non-invasive method to predict mortality risk of MI patients with AF thus covers an important unmet clinical need.

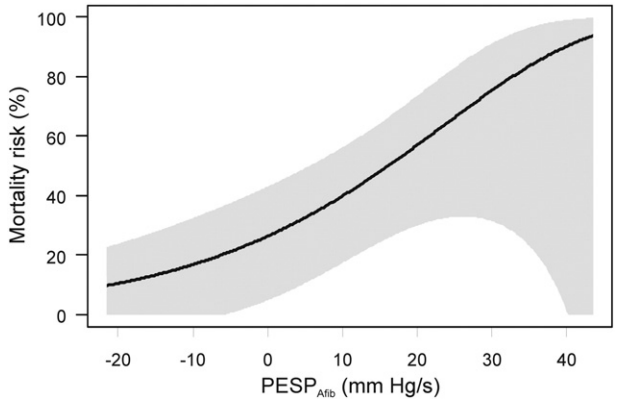

Fig. 3. Continuous association of $PESP_{Afib}$ and mortality risk. The mortality risk (black line) together with the 95% confidence interval (gray area) is shown as a function of $PESP_{Afib}$ cutoff value.

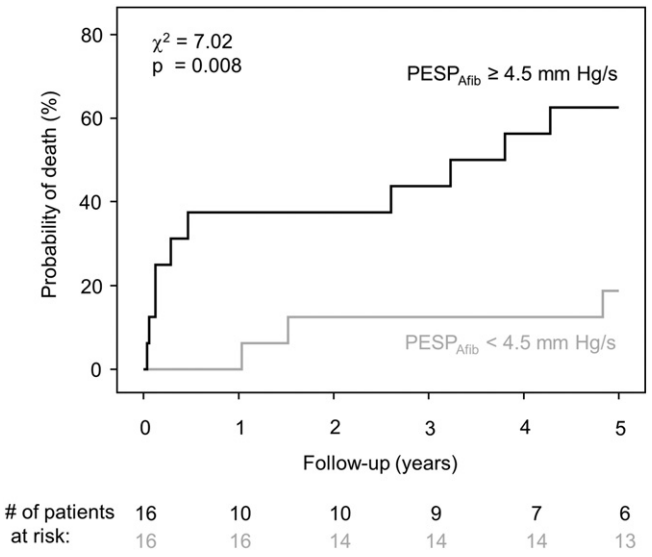

Fig. 4. Mortality risk over five years of patients stratified by $PESP_{Afib}$ dichotomized at the median (4.5 mm Hg/s) is depicted. The number of patients at risk is indicated below the graph using the same color coding.

PESP and its derivative $PESP_{Afib}$ are manifestations of the myocardial force–interval relationship (FIR). It has been shown that the FIR is a major determinant of the beat-to-beat blood pressure variability during atrial fibrillation [16–19].

The FIR is determined to a large extent by the magnitude of intracellular calcium transients in the cardiomyocytes [20]. Most experimental studies have determined FIR (typically expressed as its inverse, the force–frequency relation, FFR) under steady-state conditions by pacing the myocardium at different frequencies. In the normal heart beating within the physiological range of heart rates, this steady-state contractility increases with higher heart rates (i.e., with shorter beat-to-beat intervals). A blunted or even inverse FFR is a hallmark of failing myocardium [21]. The FIR, however, also manifests at disequilibrium when the

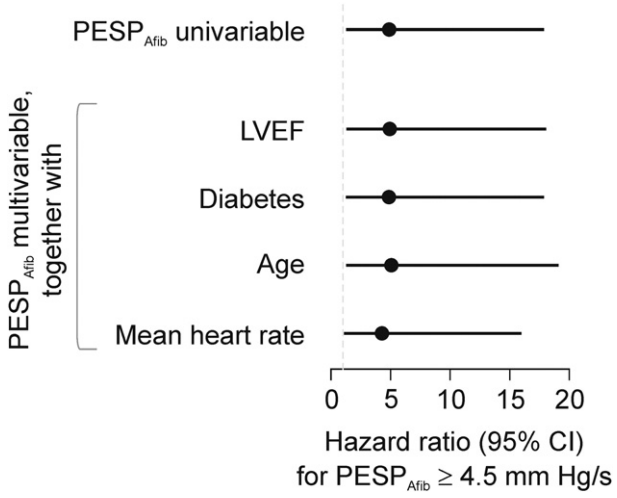

Fig. 5. Analysis for possible confounding factors. The hazard ratio and 95% confidence interval for $PESP_{Afib}$ obtained from univariable Cox analysis as well as those obtained from multivariable analyses including one of several other risk predictors (LVEF, diabetes, age, mean heart rate) are shown. The gray dashed line indicates a hazard ratio of one. $PESP_{Afib}$ remained a significant predictor of mortality in all multivariable models.

steady state of a constant heart rate is disturbed, e.g. by an ectopic beat [22] or, as investigated in the present study, by the highly-variable beat-to-beat cycle lengths during AF [16].

The increased contractility of a post-extrasystolic heartbeat can be understood on the basis of the underlying calcium signaling processes [23,24]. A premature heartbeat results in calcium influx via the plasma membrane at a time point when a relevant fraction of the ryanodine receptor calcium channels in the membrane of the sarcoplasmic reticulum (SR) is still refractory. Consequently, calcium release through the ryanodine receptors is reduced compared to normal heartbeats. In the post-extrasystolic pause, the SR calcium content is further increased due to re-sequestration by the sarco-endoplasmatic reticulum calcium ATPase (SERCA). The increased SR calcium content available for release at the post-extrasystolic heartbeat results in an augmented post-extrasystolic contraction.

In the failing myocardium, the SR calcium content is reduced, as several integral compounds of the calcium cycling system are dysregulated (e.g. leakiness of ryanodine receptors and reduced SERCA activity) [21]. Starting from this lower steady state, the relative increase of SR calcium content during the post-extrasystolic pause and, consequently, the relative potentiation of post-extrasystolic calcium release are augmented as compared to normal hearts. This is supported by both modeling studies and experimental data. For example, in a computational model of myocardial calcium handling, an attenuation of SERCA activity resulted in increased PESP [25]. In a mouse model, overexpression of the SERCA inhibitor phospholamban was associated with a reduced SR calcium content and increased PESP [26].

In the present study, as in our previous study [5], a steeper-than-normal FIR (indicated by larger-than-normal PESP or $PESP_{Afib}$) was associated with an increased mortality. Although at first sight counterintuitive, it is well established that in the failing heart, PESP is typically enhanced as compared to normal ventricles [27–31].

Further investigation of $PESP_{Afib}$ in various clinical conditions is needed. In particular, it would be appropriate to know whether treatment of acutely decompensated heart failure is accompanied by regression of $PESP_{Afib}$ values. Moreover, since the pathophysiological concept of $PESP_{Afib}$ is closely related to that of PESP, a comparison of these two parameters in patients who have both sinus rhythm and atrial fibrillation (e.g. before and after cardioversion of persistent AF or in patients with paroxysmal AF) might help for improving our understanding of the correlation of these two phenomena.

5. Limitations

The main limitations of our study are the small sample size and the retrospective nature of the analysis, which call for a prospective validation of the approach in a larger patient cohort.

$PESP_{Afib}$ was assessed on the basis of systolic blood pressure changes. Systolic blood pressure is not solely determined by the contractile state of the heart, but also affected by the compliance of the vascular system. Therefore, increased peripheral arterial resistance might contribute to the steep $PESP_{Afib}$ found in high-risk patients. The maximum systolic rise of left ventricular pressure (dP/dt_{max}) would be more closely correlated with myocardial contractility than systolic blood pressure; however, determining this parameter would require invasive catheterization of the left ventricle. If $PESP_{Afib}$ was calculated based on dP/dt_{max} taken from the non-invasive peripheral blood pressure recordings, however, we still observed a significant association with mortality, although reaching slightly lower statistical significance levels (data not shown).

Regional analysis of post-extrasystolic myocardial contractility has been used as a tool to identify "stunned" or "hibernating" myocardial regions, that are hypocontractile at rest due to ischemia and might benefit from revascularization [32]. The presence of such regions might also influence $PESP_{Afib}$ measured at the blood pressure level. A substantial fraction of the included patients were not completely revascularized at the time of the $PESP_{Afib}$ assessment, or underwent repeat revascularizations within one year (see Table 1). However, when either complete revascularization status or repeat revascularization was included in the Cox model together with $PESP_{Afib}$, only $PESP_{Afib}$ remained in the model as a significant predictor of mortality (data not shown). We conclude that regional ischemia is not a relevant confounder in our data.

We assessed $PESP_{Afib}$ during the acute hospitalization, on median 8 days (interquartile range 4–11) after the index MI. It is possible that a different timing (e.g. in the stable phase > 30 days after the MI) might influence the predictive value of the test.

The criteria for the identification of suitable heartbeat pairs qualified for $PESP_{Afib}$ assessment (RR_i as <80% and RR_{i+1} as ≥140% of $\overline{RR}$, where $\overline{RR}$ is calculated as mean of 17 surrounding RR intervals) were developed in our data set to optimize the signal-to-noise ratio. These criteria might not be universally optimum.

6. Conclusions

$PESP_{Afib}$, a measure for the force–interval relationship in patients with AF, can be derived from simultaneous ECG and blood pressure recordings. The results of this pilot study indicate that $PESP_{Afib}$ may be useful to predict adverse outcome in survivors of myocardial infarction suffering from AF.

Conflict of interest

None of the authors have any conflict of interest.

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References

[1] O. Langendorff, Ueber elektrische Reizung des Herzens, Du-Bois-Reymond's Archiv. Fur Physiologie 8 (1885) 284–287.
[2] O. Langendorff, Untersuchungen am überlebenden Säugetierherzen III. Abhandlung: Unregelmäßigkeiten des Herzschlages und ihre Ausgleichung, Pflugers Arch. Gesamte Physiol. 70 (1898) 473–486.
[3] A. Bornstein, Die Postextrasystole, Zbl. Physiol. 20 (1906) 401–405.
[4] B.F. Hoffman, E. Bindler, E.E. Suckling, Postextrasystolic potentiation of contraction in cardiac muscle, Am. J. Physiol. 185 (1956) 95–102.
[5] D. Sinnecker, R. Dirschinger, P. Barthel, A. Müller, A. Morley-Davies, A. Hapfelmeier, M. Dommasch, K.M. Huster, G. Hasenfuss, K.L. Laugwitz, M. Malik, G. Schmidt, Post-extrasystolic blood pressure potentiation predicts poor outcome of cardiac patients, J. Am. Heart Assoc. 3 (3) (2014) e000857.
[6] K.D. Varian, Y. Xu, C.A.A. Torres, M.M. Monasky, P.M.L. Janssen, A random cycle length approach for assessment of myocardial contraction in isolated rabbit myocardium, Am. J. Physiol. Heart Circ. Physiol. 279 (2009) H1940–H1948.
[7] H. Huikuri, P.K. Stein, Clinical application of heart rate variability after acute myocardial infarction, Front. Physiol. 3 (2012) 41.
[8] G. Schmidt, M. Malik, P. Barthel, R. Schneider, K. Ulm, L. Rolnitzky, A.J. Camm, J.T. Bigger Jr., A. Schömig, Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction, Lancet 353 (1999) 1390–1396.
[9] A. Bauer, M. Malik, G. Schmidt, P. Barthel, H. Bonnemeier, I. Cygankiewicz, P. Guzik, F. Lombardi, A. Müller, A. Oto, R. Schneider, M. Watanabe, D. Wichterle, W. Zareba, Heart rate turbulence: standards of measurement, physiological interpretation, and clinical use, J. Am. Coll. Cardiol. 52 (2008) 1353–1356.
[10] A. Bauer, J.W. Kantelhardt, P. Barthel, R. Schneider, T. Mäkikallio, K. Ulm, K. Hnatkova, A. Schömig, H. Huikuri, A. Bunde, M. Malik, G. Schmidt, Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study, Lancet 367 (2006) 1674–1681.
[11] R.L. Verrier, T. Klingenheben, M. Malik, N. El-Sherif, D.V. Exner, S.H. Hohnloser, T. Ikeda, J.P. Martínez, S.M. Narayan, T. Nieminen, D.S. Rosenbaum, Microvolt T-wave alternans. Physiological basis, methods of measurement, and clinical utility — consensus guideline by international society for Holter and noninvasive electrocardiology, J. Am. Coll. Cardiol. 58 (2011) 1309–1324.
[12] P. Barthel, R. Wensel, A. Bauer, A. Müller, P. Wolf, K. Ulm, K.M. Huster, D.P. Francis, M. Malik, Respiratory rate predicts outcome after acute myocardial infarction: a prospective cohort study, Eur. Heart J. 34 (2013) 1644–1650.

[13] M. Dommasch, D. Sinnecker, P. Barthel, A. Müller, R.J. Dirschinger, A. Hapfelmeier, K.M. Huster, K.L. Laugwitz, M. Malik, G. Schmidt, Nocturnal respiratory rate predicts non-sudden cardiac death in survivors of acute myocardial infarction, J. Am. Coll. Cardiol. 63 (2014) 2432–2433.
[14] D. Sinnecker, M. Dommasch, P. Barthel, A. Müller, R.J. Dirschinger, A. Hapfelmeier, K.M. Huster, K.L. Laugwitz, M. Malik, G. Schmidt, Assessment of mean respiratory rate from ECG recordings for risk stratification after myocardial infarction, J. Electrocardiol 47 (5) (2014) 700–704.
[15] K.D. Rizas, T. Nieminen, P. Barthel, C.S. Zürn, M. Kähönen, J. Viik, T. Lehtimäki, K. Nikus, C. Eick, T.O. Greiner, H.P. Wendel, P. Seizer, J. Schreieck, M. Gawaz, G. Schmidt, A. Bauer, Sympathetic activity-associated periodic repolarization dynamics predict mortality following myocardial infarction, J. Clin. Invest. 124 (2014) 1770–1780.
[16] S.M.C. Hardman, M.I.M. Noble, W.A. Seed, Postextrasystolic potentiation and its contribution to the beat-to-beat variation of the pulse during atrial fibrillation, Circulation 86 (1992) 1223–1232.
[17] S.M.C. Hardman, K.P. Pfeiffer, T. Kenner, M.I.M. Noble, W.A. Seed, Analysis of left ventricular contractile behaviour during atrial fibrillation, Basic Res. Cardiol. 98 (1994) 438–455.
[18] S.M.C. Hardman, M.I.M. Noble, T. Biggs, A. Seed, Evidence for an influence of mechanical restitution on beat-to-beat variations in haemodynamics during chronic atrial fibrillation in patients, Cardiovasc. Res. 38 (1998) 82–90.
[19] S. Suzuki, J. Araki, T. Morita, S. Mohri, T. Mikane, H. Yamaguchi, S. Sano, T. Ohe, M. Hirakawa, H. Suga, Ventricular contractility in atrial fibrillation is predictable by mechanical restitution and potentiation, Am. J. Physiol. 275 (1998) H1513–H1519.
[20] M. Endoh, Force–frequency relationship in intact mammalian ventricular myocardium: physiological and pathophysiological relevance, Eur. J. Pharmacol. 500 (2004) 73–86.
[21] G. Hasenfuss, B. Pieske, Calcium cycling in congestive heart failure, J. Mol. Cell. Cardiol. 34 (2002) 951–969.
[22] S.M.C. Hardman, Clinical implications of the interval–force relationship of the heart, Postgrad. Med. J. 70 (1994) 553–557.
[23] W.G. Wier, D.T. Yue, Intracellular calcium transients underlying the short-term force–interval relationship in ferret ventricular myocardium, J. Physiol. 376 (1986) 507–530.
[24] J.J. Rice, M.S. Jafri, R.L. Winslow, Modeling short-term interval–force relations in cardiac muscle, Am. J. Physiol. Heart Circ. Physiol. 278 (2000) H919–H931.
[25] G. Iribe, P. Kohl, D. Noble, Modulatory effect of calmodulin-dependent kinase II (CaMKII) on sarcoplasmic reticulum Ca^{2+} handling and interval–force relations: a modeling study, Phil. Trans. R. Soc. A 364 (2006) 1107–1133.
[26] B.D. Hoit, D.A. Tramuta, V.J. Kadambi, R. Dash, N. Ball, E.G. Kranias, R.A. Walsh, Influence of transgenic overexpression of phospholamban on postextrasystolic potentiation, J. Mol. Cell. Cardiol. 31 (1999) 2007–2015.
[27] W. Beck, E. Chesler, V. Schrire, Postextrasystolic ventricular pressure responses, Circulation 44 (1971) 523–533.
[28] J. Kvasnicka, B. Liander, H. Broman, E. Varnauskas, Quantitative evaluation of postectopic beats in the normal and failing human heart using indices derived from catheter-tip manometer readings, Cardiovasc. Res. 9 (1975) 336–341.
[29] J.P. Merillon, G. Motte, M.C. Aumont, C. Masquet, Y. Lecarpentier, R. Gourgon, Postextrasystolic left ventricular peak pressure with and without left ventricular failure, Cardiovasc. Res. 13 (1979) 338–344.
[30] W.A. Seed, M.I. Noble, J.M. Walker, G.A. Miller, J. Pidgeon, D. Redwood, R. Wanless, M.R. Franz, M. Schoettler, J. Schaefer, Relationships between beat-to-beat interval and the strength of contraction in the healthy and diseased human heart, Circulation 70 (1984) 799–805.
[31] A. Voss, V. Baier, A. Schumann, A. Hasart, F. Reinsperger, A. Schirdewan, K.J. Osterziel, U. Leder, Postextrasystolic regulation patterns of blood pressure and heart rate in patients with idiopathic dilated cardiomyopathy, J. Physiol. 538 (1) (2002) 271–278.
[32] M.W. Cooper, Postextrasystolic potentiation: do we really know what it means and how to use it? Circulation 88 (1993) 2962–2971.